REMARKS/ARGUMENTS

After entry of this amendment, claims 1-23 and 25-28 are pending, claims 1-12, 14, 17, 20, 23 and 25-26 having been amended, claim 24 having been previously canceled, and claim 29 having been canceled.

I. Status of the Claims

Claim 1 is amended by reorganizing the claim for clarity. Claim 1 is further amended to delete the possibility of X_3 having no amino acid. Support is provided in the specification at, e.g., page 12, the third full paragraph.

Claims 2, 4-9, 11-12, 14, 17, 20 and 25-26 are amended by reciting that the "polypeptide variant" is a "BMP or GDP polypeptide variant" and the "polypeptide" is a BMP or GDP polypeptide" for clarity. Support is provided in claim 1.

Claim 3 is amended to be in independent form. Support is provided in claim 1.

Claim 4 is further amended by introducing "that" between "in" and "said" to correct an obvious typographical error.

Claim 7 is further amended by replacing "at least 10% of the biological activity of the unaltered polypeptide" with "essentially the same receptor binding affinity to the ectodomain of BMPR-IA as BMP." Support is provided in the specification at, e.g., in Figure 4, in Examples 1 and 2, and on page 15, second full paragraph.

Claim 10 is amended to be in independent form. Support is provided in claims 1 and 8, and in Examples 1 and 2, where T3 and T4 are BMP-2 polypeptide variants.

No new matter is added by these amendments.

II. Formal Matters

In the instant Office Action, the Examiner states that claims 1-23 and 25-29 are pending, as drawn to the elected invention of SEQ ID NO:1, and claims 3 and 10 are withdrawn from examination as being drawn to a non-elected invention. Applicant respectfully submits that claims 3 and 10 are withdrawn in error. In response to the restriction requirement, Applicant elected Group I, drawn to polypeptides comprising SEQ ID NO:1. Claims 3 and 10 are drawn to the elected invention comprising SEQ ID NO:1 because the oliopeptides of SEQ ID NOs: 3 and 4 recited in claim 3 are encompassed by SEQ ID NO:1, and the polypeptides of SEQ ID NO:5 and 6 recited in claim 10 have one and two oligopeptides, respectively, encompassed by SEQ ID NO:1. Further, in the previous Office Action mailed September 29, 2004, the Examiner acknowledged that claims 3 and 10 should be allowable if written in independent form, including all of the limitations of the base claim and any intervening claims. Accordingly, Applicant respectfully requests that claims 3 and 10, which have been herein amended to be in independent form including all of the limitations of the claim 1 and intervening claim 8, be examined.

III. The Presently Claimed Invention

The presently claimed invention is directed to bone morphogenetic protein (BMP) or growth differentiation factor (GDF) polypeptide variants with increased heparin-binding ability, characterized in that at least one oligopeptide comprising the amino acid sequence $X_1X_2X_3X_4X_5X_6$ is added to, and/or inserted into, and/or substituted into a BMP or GDF polypeptide, wherein X_1 is K, R, or H; X_2 is K, R, or H; X_3 is K, R, or H; X_4 is not K, R, H, but any other amino acid; X_5 is not K, R, H, but any other or no amino acid; and X_6 = not K, R, H, but any other or no amino acid (SEQ ID NO: 1). Accordingly, all of the claimed polypeptide variants are members of the BMP or GDF family, comprising at least one oligopeptide with a structural motif having 3 positively charged (basic) amino acids followed by 1 to 3 non-positively charged (non-basic) amino acids, which have increased heparin-binding ability as compared to the unaltered BMP or GDF polypeptide.

IV. Anticipation Rejections

The rejection of claims 1, 2, 4-7, 9, 11-23 and 25-26 as being anticipated by U.S. Application Pub. No. 2001/0020086 ("the '086 application") has been maintained. The Examiner cites the '086 application as allegedly teaching the addition of heparin-binding domains to any growth factor (paragraphs [0011] and [0014]). The Examiner also alleges that claim 1 does not contain a limitation requiring that the polypeptide variant comprising SEQ ID NO:1 be added and/or inserted into a polypeptide containing a naturally occurring heparin-binding site because the limitation "wherein the polypeptide is a bone morphogenetic protein (BMP) or a growth differentiation factor (GDF)" is applicable only to subpart (iii) of the claim. Applicant traverses this rejection of the claims as they may be applied to the amended claims.

As set forth in our previous response filed October 17, 2005, the '086 application fails to anticipate claims 1-7, 9-23 and 25-26 because it does not teach every element of the presently claimed invention. Specifically, the '086 application does not teach adding heparin-binding domains to heparin-binding growth factors, in general, or to BMP or GDF family members, in particular. The use of the term "novel" in qualifying "domain" in paragraph [0011] indicates that the '086 application only contemplated the addition of heparin-binding domains to growth factors lacking such domains. The entire '086 application does not mention adding a heparin-binding domain to a heparin-binding growth factor. In particular, in paragraph [0014], relied upon by the Examiner, a list of heparin-binding growth factors is recited; however, this paragraph provides no teaching or suggestion that heparin-binding domains are to be added to these growth factors. Elsewhere in the '086 application, the addition of heparin-binding domains to growth factors that lack such domains is discussed. For example, in paragraph [0004], it is stated that "if the protein to be bound does not contain a native heparin-binding sequence, a fusion protein can be constructed containing the native protein sequence and a synthetic heparin-binding domain." In paragraph [0078], Example 4 discusses adding a heparin-binding domain to growth factors that do not spontaneously bind heparin. In paragraphs [0097] and [0109], Examples 7 and 8 describe introducing a heparin-binding domain into nerve growth factor (NGF), which lacks a naturally-occurring heparin-binding domain. Thus, the '086 application taken as a whole does not teach or suggest adding heparin-binding domains to the species of

growth factors that already bind heparin in their native form. In particular, the '086 application does not indeed disclose adding heparin-binding domains to BMP or GDF polypeptides.

The Examiner's allegation that claim 1 is not limited to adding, inserting or substituting an oligopeptide comprising SEQ ID NO:1 into a BMP or GDF polypeptide is based on a misreading of the claim. Although disagreeing with the Examiner's interpretation, Applicant has amended the claims to clarify that the polypeptide is a BMP or GDF polypeptide and the polypeptide variant is a BMP or GDF polypeptide variant. Accordingly, claim 1 is clearly limited to adding and/or inserting and/or substituting at least one oligopeptide comprising SEQ ID NO:1 into a BMP or GDF polypeptide, both of which already containing a naturally occurring heparin-binding domain.

For the foregoing reasons, Applicant respectfully requests that the rejection of claims 1, 2, 4-7, 9, 11-23 and 25-26 as being anticipated by the '086 application be withdrawn.

Claim 27 is rejected as being anticipated by the '086 application. The Examiner cites the '086 application as allegedly teaching heparin-binding growth factor fusion protein constructs, transformed vectors, plasmids and expression in bacterial systems. Claim 27 is not anticipated by the '086 application for at least the same reasons as those for independent claim 17, from which claim 27 depends. Accordingly, Applicant respectfully requests that the rejection of claim 27 as being anticipated by the '086 application be withdrawn.

V. Obviousness Rejections

The rejection of claim 8 as being unpatentable over the '086 application in view of Linkhart et al., *Bone* 19:1S-12S, 1996 ("Linkhart") has been maintained. The Examiner cites the '086 application as allegedly teaching heparin-binding growth factors non-covalently bound in gels and matrices, and that careful selection of the enzymatic degradation site of the matrices can be accomplished by a stated means to permit sequestration of proteins and targeted release at specific sites. The Examiner also cites the '086 application as allegedly teaching adding additional heparin-binding sites to proteins already containing such sites because a high excess

of heparin-binding sites "is essential to ensure that the growth factors do not diffuse far before they bind to the matrix again" (paragraph [0013]).

The Examiner alleges that, by combining the teachings of the '086 application and Linkhart, it would have been obvious to the skilled artisan to use the heparin-binding sequestration technique of the '086 application to target BMPs and GDFs to the bone, as taught by Linkhart.

The motivation asserted by the Examiner in the Office Action of September 29, 2004 to combine the teachings of the '086 application and Linkhart to add additional heparin-binding domains to BMPs is that the '086 application teaches ways to modify growth factors so that they may be attached to matrices, and Linkhart teaches that such an attachment is useful for BMPs.

Applicant respectfully traverses this rejection.

First, as detailed above, the Examiner has misinterpreted the teachings of the '086 application. As discussed above, the '086 application does not teach growth factors with heparin-binding domains as a species of growth factors into which further heparin-binding domains should be introduced. This deficiency in the '086 application is not compensated by Linkhart. The concluding statement in Linkhart that "one of the most important developments in the future is likely to be methods for delivery of the growth factors to bone at *specific* sites" (emphasis added) would not have motivated the skilled artisan to add additional heparin-binding sites to BMPs absent some teaching or suggestion that such addition would be effective for *specific* targeting to the bone. There is no teaching or suggestion in either the '086 application or Linkhart that BMPs with additional heparin-binding domains would be targeted to *specific* sites in bone.

Second, the Examiner has failed to provide any reasoning to rebut the arguments set forth by Applicants in the previous response that the skilled artisan lacked any motivation or incentive to combine the teachings of the '086 application and Linkhart to arrive at the presently

claimed invention. In particular, the Examiner has failed to set forth adequate objective evidence or reasoning to combine these teachings. The mere fact that the references can be combined or modified does not render the combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430. The Examiner has failed to point out any teaching or suggestion in either the '086 application or Linkhart that *specific* targeting of BMP proteins to bone, as desired by Linkhart, would be achieved by adding additional heparin-binding domains, as allegedly taught by the '086 application. Consequently, the Examiner has not met her burden of proof to establish *prima facie* obviousness.

Third, the Examiner cites paragraph [0013] of the '086 application but draws the wrong conclusion. The Examiner alleges that the '086 application teaches adding additional heparin-binding domains to proteins already containing heparin-binding sites because a high excess of heparin-binding sites "is essential to ensure that the growth factors do not diffuse far before they bind to the matrix again." Contrary to the Examiner's assessment, paragraph [0013] merely explains that an excess of heparin-binding sites is essential to allow growth factors to bind to the matrix. This disclosure neither suggests nor implies that additional heparin-binding sites should be introduced into a heparin-binding growth factor. The Examiner has interpreted this paragraph out of context. The following paragraph [0014] lists growth factors containing naturally occurring heparin-binding domains, and paragraph [0016] points out that heparin can be either covalently or non-covalently bound to fibrin gels to provide new functionality to the new materials. It is the binding of heparin to the matrix which allows the fibrin matrix to bind heparin-binding proteins, including growth factors, in a manner which does not affect the protein, while at the same time preventing the protein from escaping the gel. Given this context, paragraph [0013] cannot be interpreted to suggest or imply that additional heparin-binding sites should be introduced into growth factors. Based on the disclosure of the '086 application, the skilled artisan can only conclude that there are already many heparin molecules in the matrix to which a growth factor can attach, which in turn effectively prevents the growth factors from diffusing out of the matrix. Thus, the skilled artisan would have concluded from the '086

application that it would be superfluous to introduce additional heparin-binding domains into a heparin-binding growth factor.

Fourth, biomaterials may well be equipped with additional heparin-binding sites. The approach discussed in the '086 application may be useful when attempting to generate enhanced heparin-binding in gels. Notably, such an approach is only useful when using proteins that, by virtue of their nature, are able to bind to heparin. This situation, however, does not apply to the presently claimed invention, which relates to BMP or GDF polypeptide variants that have been designed to enhance the binding of these growth factors to heparinic sites of heparin-like molecules naturally occurring in the extracellular matrix.

Fifth, the Examiner is reminded that the '086 application only discloses the use of heparin-binding growth factors being non-covalently linked to a matrix or gel, whereas the subject matter of the presently claimed invention relates to the use of BMP- or GDF-derived polypeptide variants in the absence of such matrices or gels.

Taken together, the Examiner's analysis can only be regarded as being taken from a hindsight perspective and with knowledge of the presently claimed invention in mind. This explains why the Examiner failed to appreciate the non-obviousness underlying the presently claimed invention. In view of the above arguments, the skilled artisan having knowledge of the '086 application would not have been motivated to modify growth factors in a way as to arrive at, rather than being led away from, the presently claimed invention. Because Linkhart does not compensate for the deficiencies in the disclosure of the '086 application, Applicant respectfully submits that the presently claimed invention is non-obvious over the cited art and respectfully requests that the rejection of claim 8 as being unpatentable over the '086 application in view of Linkhart be withdrawn.

Claims 1, 2, 4-9, 11-23 and 25-28 are rejected as being unpatentable over the '086 application in view of Ruppert et al., *Eur. J. Biochem.* 237:295-302, 1996 ("Ruppert"). The Examiner cites the '086 application as above, acknowledging that the '086 application does not

teach the process of producing a polypeptide variant using CHO cells. The Examiner cites the Ruppert as allegedly teaching the BMP-2 variant EHBMP-2, which purportedly contains the heparin-binding sequence KKTQL (conforming to the limitations of SEQ ID NO:1) by substituting the N-terminal 12 amino acids of BMP-2 with a dummy sequence of comparable length and polarity. Ruppert allegedly teaches: (1) that EHBMP-2 exhibits 15-20 fold increased specific activity compared to BMP-2; (2) the importance of the 3-D structure of BMP-2 and the conformation adopted by the N-terminal heparin-binding sites; (3) and the importance of the multiple basic triplets in the heparin-binding sequence of BMP-2, as well as other BMP proteins and GDF-5.

The Examiner alleges that it would have been obvious to make polypeptide variants with increased heparin-binding ability, with a reasonable expectation of success, by combining the teachings of the '086 application and Ruppert, which allegedly shows that mutating the N-terminal region of BMP-2 increases the specific activity of heparin-binding in the EHBMP-2 variant and such growth factor variants can be successfully produced in *E. coli*.

The motivation asserted by the Examiner to combine the teachings of the '086 application and Ruppert is that the skilled artisan would have been motivated to produce heparin-binding polypeptide variants in CHO cells to determine the effects of post-translational modifications on the variants.

Applicant respectfully traverses this rejection.

As an initial matter, the Examiner alleges that the EHBMP-2 variant contains the heparin-binding sequence KKTQL, which conforms to the limitations of SEQ ID NO:1. As described in detail below, the Examiner is mistaken because the EHBMP-2 variant does not bind heparin. Further, the sequence KKTQL does not conform to the limitations of SEQ ID NO:1, as recited in amended claim 1 because SEQ ID NO:1 requires three basic amino acids, not two as found in the EHBMP-2 variant.

It is clear that the Examiner has not fully appreciated the teachings of Ruppert. Ruppert discusses a BMP-2 variant in which the N-terminal moiety (amino acids 1 to 12) has been exchanged for a random sequence of equal length and polarity. As is apparent from the Ruppert abstract, the heparin-binding ability of the resultant EHBMP-2 variant is negligible compared to the parent BMP-2. As a consequence, rather than inserting a heparin-binding site, the naturally occurring heparin-binding site in BMP-2 has actually been removed. Thus, Ruppert does not disclose a polypeptide variant according to amended claim 1, i.e., a BMP or GDF polypeptide variant with increased heparin-binding ability, but, rather, discloses a BMP variant with negligible heparin-binding ability. Accordingly, Ruppert does not teach or suggest BMP or GDF polypeptide variants with increased heparin-binding ability. As a consequence, Ruppert could not have motivated the skilled artisan to add heparin-binding domains to BMP or GDF polypeptides, thereby increasing heparin-binding ability as recited in amended claim 1.

Not only does Ruppert not teach or suggest adding heparin-binding domains to growth factors, it actually teaches away from the presently claimed invention. Despite the fact that the EHBMP-2 variant does not bind heparin, in Figure 6 Ruppert demonstrates that the activity of this variant is actually stimulated by heparin. Thus, Ruppert reports that the activity of a growth factor can be stimulated by removal of its heparin-binding domain. As such, the skilled artisan would have had no motivation to combine the teachings of the '086 application with that of Ruppert because the '086 application purportedly teaches the advantage of adding a heparin-binding domain to a growth factor, whereas Ruppert discusses an advantage of removing a heparin-binding domain from a growth factor.

Based on the foregoing, Applicant respectfully requests that the rejection of claim 8 as being unpatentable over the '086 application in view of Ruppert be withdrawn

Claim 29 is rejected as being unpatentable over the '086 application in view of Meddahi et al., *Path. Res. Pract.* 190:923-928, 1994.

Applicant has canceled this claim, thereby rendering moot this ground of rejection.

VI. Enablement Rejections

The rejection of claims 1, 2, 4-9, 11-23 and 25-26 as lacking enablement has been maintained. The Examiner alleges that the claims encompass many more proteins, sequences and motifs than Applicant has taught in the specification. In particular, the Examiner alleges that Applicant has failed to teach how to make and use each claimed variant, which purportedly includes all proteins including a consensus sequence comprising SEQ ID NO:1. The Examiner also alleges that the disclosed species does not predict the genus, the genus encompassing a vast number of proteins (allegedly *any* protein so long as it comprises at least 2 to 3 basic amino acids followed by 1 to 3 non-basic amino acids). The Examiner alleges that undue experimentation would be required for the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant respectfully traverses this rejection as it may be applied to claims 1, 2, 4-9, 11-23 and 25-26 as amended.

The Examiner alleges that "due to the large quantity of experimentation necessary to generate the numerous derivatives recited in the claimed and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Applicant respectfully disagrees for the following reasons.

First, the presently claimed invention is not directed to *any* protein comprising at least 2 to 3 basic amino acids followed by 1 to 3 non-basic amino acids, as alleged by the

Examiner. Amended claim 1 is directed to BMP or GDF variant polypeptides with increased heparin-binding ability in which at least one oligopeptide comprising 3 basic amino acids followed by 1 to 3 non-basic amino acids is added to, and/or inserted into, and/or substituted into a BMP or GDF polypeptide. Therefore, the genus is not nearly as vast as alleged by the Examiner. The claimed genus encompasses only two families of growth factors, BMP and GDF, which are well-defined structurally and functionally. Moreover, the oligopeptide comprising SEQ ID NO:1 has a clearly recognizable structural motif and a defined function.

Second, as *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), makes clear, the issue for enablement is not whether any experimentation is needed, but whether the experimentation needed is undue. The Examiner has not alleged that the experiments needed to determine whether an oligopeptide encompassed by SEQ ID NO:1 increases heparin-binding ability of a BMP or GDF polypeptide require anything other than routine experimentation. In fact, the previous Examiner acknowledged the simplicity of making and assaying members of the claimed genus. As such, even if the number of encompassed BMP or GDF polypeptide variants is very large, mere routine experimentation would be required to determine if any oligopeptide that satisfies the requirements of SEQ ID NO:1 confers the desired activity. An earlier response filed April 4, 2005 outlines the routine steps disclosed in the specification that would allow one skilled in the art to screen a reasonable number of BMP or GDF polypeptide variants for increased heparin-binding ability.

Third, the Examiner's concern regarding the lack of direction/guidance presented in the specification as to which structural features are required to provide activity was addressed by the previous response, in which Applicant explained that the skilled artisan would immediately recognize the essential feature of the structural motif of SEQ ID NO:1. As amended herein, this structural motif is: (1) a specific charge distribution of 3 positively charged (basic) amino acids, (2) followed by 1 to 3 non-positively charged (non-basic) amino acids, (3) wherein the positively charged motif is complementary to the negatively charged heparin or heparin-like substances. Armed with this clear definition of SEQ ID NO:1, the skilled artisan could determine by mere inspection of the amino acid sequence whether any particular

oligopeptide has the claimed structural motif. The Examiner has not set forth any objective evidence or reasoning why the skilled artisan would not recognize this structural motif, or why the skilled artisan would not expect this structural motif to be capable of binding heparin when added to, inserted into or substituted into a BMP or GDF polypeptide.

Fourth, the Examiner is mistaken in her statement that there is an absence of working examples in the specification. Examples 1 and 2 describe two BMP-2 variants, T3 and T4, which contain one and two oligopeptides comprising SEQ ID NO:1, respectively, near the N-terminus. Both T3 and T4 have increased heparin-binding ability compared to BMP-2.

Fifth, the nature of the invention is not as complex, and the effects of mutation on protein structure and function are not as unpredictable, as alleged by the Examiner. The presently claimed invention is directed to BMP or GDF polypeptide variants with increased heparin-binding ability. Although the number of encompassed polypeptide variants is arguably large, there is nothing particularly complex about the claimed invention. Applicant has determined that growth factor variants with increased heparin-binding ability can be generated by introducing a heparin-binding domain into growth factors already containing such a domain, and that such growth factor variants have useful biological properties *in vivo*.

The alleged complexity of the nature of this invention is introduced by the Examiner, who recites various references in support of her contention that particular regions of a protein can tolerate only relatively conservative substitutions or no substitutions. As a result, the Examiner alleges that the skilled artisan could not, without undue experimentation, determine the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions. The Examiner seems to be referring to the situation where the skilled artisan is particularly concerned about the loss of a function or an activity resulting from adding, inserting or substituting amino acids in a target protein. Although not agreeing or disagreeing with the Examiner's contention, Applicant respectfully submits that the situation in the instant case is different. Here, the skilled artisan is particularly concerned with increasing heparin-binding ability as a result of adding, inserting, or substituting an oligopeptide comprising

SEQ ID NO:1 into a BMP or GDF polypeptide. The skilled artisan, armed with the specification and knowledge of the structure-function relationships of BMP or GDF polypeptides, would be able to determine without undue experimentation where to add, insert, or substitute a heparin-binding site into the polypeptide in such a way as to increase heparin-binding ability, while retaining, at least to some degree, the biological activity of the unaltered polypeptide (e.g., receptor binding activity). Mere routine experimentation would be required to screen BMP or GDF polypeptide variants for receptor binding or other biological activity, using assays in this disclosure or known in the art. Accordingly, the Examiner's concerns regarding the complexity of the nature of the invention and unpredictability in the art are not applicable in the instant case.

Sixth, the Examiner's statement that the claims fail to recite any structural or functional limitations is incorrect. The polypeptide variants of the presently claimed invention are structurally limited to a known class of proteins, namely, members of the BMP or GDF families. This structural limitation is inherent in the recitation of BMP or GDF polypeptides in the claims. The polypeptide variants are functionally limited to BMP or GDF polypeptide variants that have increased heparin-binding ability.

The test under *In re Wands* is not whether each and every possible BMP or GDF polypeptide variant within the present claims has increased heparin-binding ability, but rather whether it is feasible to screen a reasonable number that do without undue experimentation. Here, a reasonable number of BMP or GDF polypeptide variants can be screened for heparin-binding activity by repetition of routine steps. The previous Examiner has already acknowledged the simplicity of making and assaying members of the claimed genus. There is nothing difficult in making BMP or GDF polypeptide variants falling in the scope of amended claim 1. Armed with the clear definition of the oligopeptides of SEQ ID NO:1, one would know whether any oligopeptide falls within the scope of the claim. The claimed polypeptides, members of the BMP or GDF family, are well-known in the art. Mere standard molecular biology techniques are required to make the claimed BMP or GDF polypeptide variants, and there is nothing difficult in testing the heparin-binding activity of the claimed polypeptide variants. The disclosure provides simple heparin-binding assays, which are well-known in the art. Thus, a reasonable number of

BMP or GDF polypeptide variants having heparin-binding activity would be obtained by routine molecular biology and a simple *in vitro* assay. As held by *Wands,* practitioners of the art are prepared to undertake this type of screening to identify molecules having a desired property.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 2, 4-9, 11-23 and 25-26 as lacking enablement be withdrawn.

The rejection of claim 7 as lacking enablement has been maintained. The Examiner contends that Applicant's assertion that SEQ ID NO:1 has biological activities similar to known heparin-binding sites cannot be accepted in the absence of supporting evidence because the relevant literature provides examples of polypeptide families wherein individual members have distinct and sometimes even opposite biological activities. As a result, the Examiner alleges that the specification fails to teach the skilled artisan how to make the claimed polypeptide variants retaining at least 10% biological activity of, and at least 90% homology to, the unaltered polypeptide without resorting to undue experimentation to determine what the specific biological activities of the variant are. The Examiner alleges that the specification fails to provide the skilled artisan with sufficient guidance to use the claimed polypeptide variants for any purpose. The Examiner alleges that undue experimentation would be required for the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant respectfully traverses this rejection as it may be applied to claim 7. As amended, claim 7 requires that at least one oligopeptide satisfying the requirements of SEQ ID NO:1 be added to, inserted into and/or substituted into a BMP or GDF polypeptide such that the resultant BMP or GDF polypeptide variant has increased heparin-binding ability, while retaining essentially the same receptor binding affinity to the ectodomain of BMPR-IA as BMP, and at least 90% homology to the unaltered BMP or GDF polypeptide.

The Examiner alleges that "due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide variants such that it can be determined how to use the claimed polypeptide variants showing at least 10% of the biological

activity of the unaltered peptide and at least 90% homology to the unaltered polypeptide, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Applicant respectfully disagrees for the following reasons.

The Examiner alleges that a large quantity of experimentation is necessary to determine an activity or property of the disclosed polypeptide variants such that it can be determined how to use the claimed polypeptide variants showing at least 10% of the biological activity of the unaltered peptide and at least 90% homology to the unaltered polypeptide. As amended, claim 7 recites a BMP or GDF polypeptide variant with increased heparin-binding ability, essentially the same receptor binding affinity to the ectodomain of BMPR-IA as BMP, and at least 90% homology to the unaltered BMP or GDF polypeptide. As discussed in the previous response, claims of this type specifying polypeptide variants constrained by 90% homology and retention of some biological activity have been routinely granted by the PTO. As discussed above, under *In re Wands*, the issue for enablement is not whether any experimentation is needed, but whether the experimentation needed is undue. Here, the Examiner has not alleged that making BMP or GDF polypeptide variants or testing these variants for heparin-binding ability requires anything other than routine experimentation. The Examiner has also not alleged that testing BMP or GDF polypeptide variants with increased heparin-binding ability for receptor binding affinity to the ectodomain of BMPR-IA as BMP, as exemplified in the specification, requires anything more than routine experimentation. The Examiner has failed to explain why a large quantity of routine experimentation renders the experimentation undue.

The key to applying the enablement requirement of 35 U.S.C. § 112 is to focus on the inventive features of the claims and not on ancillary aspects. There are legal precedents for this approach to applying the enablement requirement. With regard to the amount of enablement

required for inventive features of a claim versus the amount of teaching needed to describe non-inventive features of a claim, there are at least three important court decisions which expressly relax the enablement requirement for non-inventive aspects of patent claims: *In re Lange*, 209 USPQ 288 (CCPA, 1981); *In Application of Fuetterer*, 138 USPQ 217 (CCPA 1963); and *Application of Herschler*, 200 USPQ 711 (CCPA 1979).

In *Lange*, the invention related to use of electronegative gases to coat electrical devices to dampen arcing (sparks). The Examiner noted that the claims were broad enough to read on casting of electrodes and that the disclosure was limited to coating of preexisting electrodes. Convinced that this single species was not easily obtainable, the Examiner refused to allow the claims due to overbreadth. In rejecting the position of the Patent Office, the CCPA noted that the invention is the use of the gases to dampen sparks. No claim was drawn to casting of electrodes. The entire claims were allowed and the CCPA stated that "although appellant can be required to limit his claims to that subject area which is adequately disclosed, the existence of species which are not adequately disclosed does not require that the entire application be found nonenabling. See In re Cook, 58 CCPA 1049, 439, F.2d 730, 169 USPQ 298 (1971). This is especially true in this case where, as stated by appellant at oral argument, the method of forming the electrodes is **not the inventive principle.**" (Emphasis added).

In *Herschler*, the applicant had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing a single steroid (dexamethasone 21-phosphate) supported a claim to the genus of all steroids. Citing *Fuetterer*, the court explained that Herschler's claims were not drawn to a novel steroid but to the method of administration of steroids. As long as the class of steroids could be expected to be carried across the skin by DMSO, the claim could encompass any steroid, known or unknown. As in *Fuetterer*, the CCPA reminded the Patent Office that the inventive principle was a method of administration of steroids and that the specific steroid exemplified was not the point of patentability.

Here, Applicant is claiming modifications of known proteins, namely, variants of BMP or GDF polypeptides with increased heparin-binding ability; however, the known proteins are not the invention. In *Herschler*, the invention was a method of passing steroids through the skin, and the claims were appropriately not limited to the exemplified steroid. Similarly, this invention lies in increasing heparin-binding ability of heparin-binding growth factors. The claims are composition claims drawn to variants of BMP or GDF polypeptides, not the BMP or GDF polypeptides themselves, and, thus, are not appropriately limited to just the exemplified polypeptide variants. As in the cited case law, the enablement requirement to be applied should relaxed for claims to a modification of a known protein, as compared to the situation if we had identified this known protein and tried to claim it. All of the above is to say nothing more than that the scope of the claims must *reasonably* match the scope of enablement.

The Examiner alleges that the specification lacks direction/guidance regarding how to use the claimed polypeptide variants, and lacks working examples. Contrary to the Examiner's allegation, the specification provides two working examples, T3 and T4, which are BMP-2 polypeptide variants comprising one and two oligopeptides comprising SEQ ID NO:1, respectively. The specification describes how to make BMP-2 polypeptide variants, and how to test the variants for (1) heparin-binding activity, (2) binding to the ectodomain of the BMP receptor BMPR-IA, (3) stimulation of proteogylcan synthesis in chicken embryo limb buds, and (4) induction of alkaline phosphatase activity in mouse C2C12 cells. Thus, the specification provides direction/guidance and working examples as to how to use the claims BMP or GDF polypeptide variants.

The Examiner alleges that biological activity cannot be predicted based on structural similarity. The Examiner's contention that Applicant's assertion that "SEQ ID NO:1 has biological activities similar to known heparin-binding sites cannot be accepted in the absence of supporting evidence" is not applicable in the instant case. First, Applicant provides two examples demonstrating the heparin-binding ability of oligopeptides having the structural motif of SEQ ID NO:1. Second, the importance of the multiple basic triplets in the heparin-binding

sequence of BMP-2, as well as other BMP family members and GDF-5, which are encompassed by SEQ ID NO:1, has been recognized by Ruppert. Third, the claims do not require every BMP or GDF polypeptide variant comprising an at least one oligopeptide comprising SEQ ID NO:1 have increased heparin-binding ability. Fourth, the Examiner's allegation that heparin-binding activity (of an oligopeptide comprising SEQ ID NO:1) cannot be predicted based on structural similarity appears to be based on supposition, rather than objective evidence. The Examiner has not pointed to any evidence in the cited references that would lead the skilled artisan to conclude that an oligopeptide defined by SEQ ID NO:1 would not bind heparin. More than the Examiner's supposition is required to support an enablement rejection. Finally, as discussed above, the enablement test under *In re Wands* is not whether each and every possible BMP or GDF polypeptide variant within the present claims has increased heparin-binding ability, but rather whether it is feasible to screen a reasonable number that do without undue experimentation.

The Examiner alleges that the claims fail to recite particular biological activities and also embrace a broad class of structural fragments and variants. As amended, claim 7 recites that the BMP or GDF polypeptide variant has increased heparin-binding ability, essentially the same receptor binding affinity to the ectodomain of BMPR-IA as BMP, and at least 90% homology to the unaltered BMP or GDF polypeptide. Moreover, as amended, the breadth of the structural motif defined by SEQ ID NO:1 is considerably smaller than alleged by the Examiner.

Based on the foregoing, Applicant respectfully requests that the rejection of claim 7 as lacking enablement be withdrawn.

VII. Written Description Rejection

The rejection of claims 1, 2, 4-9, 11-23 and 25 as lacking written description has been maintained. The Examiner first alleges that the claimed genus is not limited in its structural requirements because the claims do not contain a limitation requiring that the polypeptide variants of SEQ ID NO:1 could be added and/or inserted into a polypeptide containing a naturally occurring heparin-binding site. According the Examiner's reading, claim 1 reads on

adding/inserting heparin-binding sites into polypeptides that do not naturally contain a heparin-binding site. The Examiner next alleges that only a single species is disclosed that is within the scope of the claimed genus, and that "Applicant has not adequately described all possible polypeptide variants comprising SEQ ID NO:1 for all known polypeptides in any species." Finally, the Examiner alleges that there is substantial variability among the species, so that in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. Applicant respectfully traverses this rejection as it may be applied to claims 1, 2, 4-9, 11-23 and 25 as amended.

The Examiner acknowledges that the claimed genus would not be so limited in its structural requirements because there are restrictions on size, composition and order of amino acids "but for Applicant's use of the term "comprising" in claim 1. According to the Examiner, the use of "comprising" renders the claims open to the possibility that a polypeptide variant of claim 1 may be derived from a polypeptide that does not naturally contain a heparin-binding site. As clarified by amendment, claim 1 recites a BMP or GDF polypeptide variant having increased heparin-binding ability comprising at least one oligopeptide comprising SEQ ID NO:1 added to, and/or inserted into, and/or substituted into a BMP or GDF polypeptide. Thus, the claimed polypeptide variant is derived from a polypeptide having a naturally occurring heparin-binding site because the polypeptide is limited to BMP or GDF family members, all of which are heparin-binding growth factors.

The presently claimed genus, encompassing oligopeptides satisfying the requirements of SEQ ID NO:1, is limited in its structural requirements. The oligopeptides of SEQ ID NO:1 are limited in both size and composition: they must be 4 to 6 amino acids in length, and include 3 positively charged (basic) amino acids, followed by 1 to 3 non-positively charged (non-basic) amino acids. Thus, the claimed genus is restricted both in size and composition, as well as in the order of basic and non-basic amino acids. As discussed in the previous response, this feature of these oligopeptides, where non-basic amino acids follow basic amino acids, provides the key component of the structural requirement of the claimed genus, namely, the provision of a positively charged motif that is complementary to the negatively

charged heparin or heparin-like substances to which the oligopeptides bind. Thus, the claimed genus is not so limited in its structural requirements because of restrictions on size, composition, and order of amino acids.

The claimed genus is also not so highly variant as the Examiner contends. First, the claimed genus is limited to polypeptide variants of only two families of heparin-binding growth factors, BMP and GDF. Second, only a small percentage of the possible oligopeptides satisfy the structural requirements of SEQ ID NO:1. As amended, SEQ ID NO:1 comprises tetrapeptides (X_1-X_4), pentapeptides (X_1-X_4 and either X_5 or X_6) and hexapeptides X_1-X_6. X_1-X_3 can be H, R or K, and X_4-X_6 can be any of the other 17 amino acids. As a result, 459 of 16,000 tetrapeptides, 8803/320,000 pentapeptides, and 149,693 of 6,400,000 hexapeptides, overall less than 3% of the possible oligopeptides are encompassed by SEQ ID NO:1. Thus, the claimed genus is not highly variant because there are restrictions on the polypeptide and on the number of possible oligopeptides that satisfy the requirements of SEQ ID NO:1.

Adequate written description can be provided by description of structural features commonly possessed by members of the claimed genus that distinguishes them from others. *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, (Fed. Cir. 1997). Here, the specification and claims describe structural features commonly possessed by the oligopeptides of SEQ ID NO:1, as required by *Lilly*. In particular, the oligopeptides of SEQ ID NO:1 have a common structural motif, namely, the combination of X_1-X_3 and X_4-X_6, wherein X_1-X_3 includes positively charged (basic) amino acids capable of interacting with the negatively charged sulfated glucosaminoglucanes, and X_4-X_6 includes 1 to 3 non-positively charged (non-basic) amino acids. The specification and claims also described the structural features commonly possessed by the claimed polypeptide variants, namely, members of the BMP or GDF family of heparin-binding growth factors with increased heparin-binding ability resulting from adding, and/or inserting, and/or substituting at least one oligopeptide comprising a defined structural heparin-binding motif.

The Examiner's allegation that the single disclosed species of the claimed genus does not provide an adequate description of the genus is again based on a misreading of the claim. Regarding the genus of heparin-binding sequences, Applicant respectfully submits that the structural requirements of SEQ ID NO:1, as described in detail above, are indeed sufficient to characterize and identify a genus of heparin-binding sequences that is neither highly variant nor so limited in its structural requirements. Regarding the genus of polypeptide variants, the genus of BMP and GDF polypeptide variants is described by the existence of many known BMP and GDF family members. Applicant respectfully submits that the BMP-2 variants described in the specification are representative of the genus because all other species in the genus are variants of polypeptides in the same gene family as BMP-2, and are thus sufficient to characterize and identify a genus of polypeptide variants.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 2, 4-9 and 11-23 and 25 as lacking written description be withdrawn.

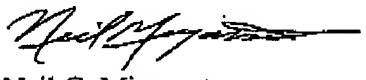
VIII. Indefiniteness Rejection

Claim 29 is rejected as being indefinite. The Examiner alleges that the phrase "physiologically compatible additives" is not defined in the specification or otherwise clarified what is meant by the term.

Applicant has canceled this claim, thereby rendering moot this ground of rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Neil G. Miyamoto
Reg. No. 50,370

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
NGM:ym
60730293 v1